Science of the Total Environment 789 (2021) 147816

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Modelling the SARS-CoV-2 outbreak: Assessing the usefulness of protective measures to reduce the pandemic at population level

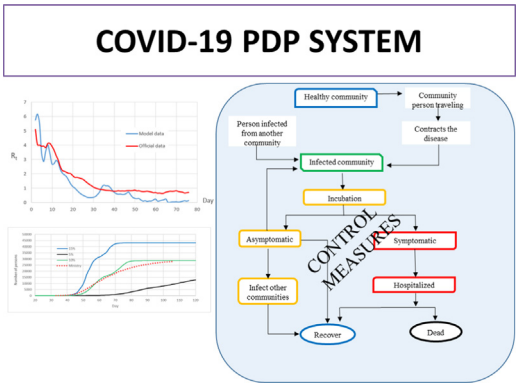
Mª. Àngels Colomer [a], Antoni Margalida [b,c], Francesc Alòs [d], Pilar Oliva-Vidal [b,c], Anna Vilella [e], Lorenzo Fraile [b,f,*]

[a] Department of Mathematics, ETSEA, University of Lleida, 25198 Lleida, Spain
[b] Department of Animal Science, ETSEA, University of Lleida, 25198 Lleida, Spain
[c] Institute for Game and Wildlife Research, IREC (CSIC-UCLM-JCCM), 13005 Ciudad Real, Spain
[d] Primary Health Center, Passeig Sant Joan, Barcelona, Spain
[e] Hospital Clinic de Barcelona, Barcelona, Spain
[f] Agrotecnio, University of Lleida, 25198 Lleida, Spain

HIGHLIGHTS

- Lockdown and contact reduction measures only delay the spread of the virus in the population
- Our model predicted that 56% of the Spanish population would have been infected.
- With protective measures could be reduced by 34% and until 13.3% with 75% of the population vaccinated.
- The combination of protective measures and vaccination (75%) reduces population infection until 7.9%
- Mortality falls from 0.41% (without protective measures) to 0.06% by combining vaccination (75%) and protective measures.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 2 March 2021
Received in revised form 28 April 2021
Accepted 12 May 2021
Available online 21 May 2021

Editor: Lotfi Aleya

Keywords:
COVID-19
Vaccination
Pandemic management
Pandemic control measures
Population dynamics P system model

ABSTRACT

A new bioinspired computational model was developed for the SARS-CoV-2 pandemic using the available epidemiological information, high-resolution population density data, travel patterns, and the average number of contacts between people. The effectiveness of control measures such as contact reduction measures, closure of communities (lockdown), protective measures (social distancing, face mask wearing, and hand hygiene), and vaccination were modelled to examine possibilities for control of the disease under several protective vaccination levels in the population. Lockdown and contact reduction measures only delay the spread of the virus in the population because it resumes its previous dynamics as soon as the restrictions are lifted. Nevertheless, these measures are probably useful to avoid hospitals being overwhelmed in the short term. Our model predicted that 56% of the Spanish population would have been infected and subsequently recovered over a 130 day period if no protective measures were taken but this percentage would have been only 34% if protective measures had been put in place. Moreover, this percentage would have been further reduced to 41.7, 27.7, and 13.3% if 25, 50 and 75% of the population had been vaccinated, respectively. Finally, this percentage would have been even lower at 25.5, 12.1 and 7.9% if 25, 50 and 75% of the population had been vaccinated in combination with the application of protective measures, respectively. Therefore, a combination of protective measures and vaccination would be highly efficacious in decreasing not only the number of those who become infected and subsequently

* Corresponding author at: Department of Animal Science, ETSEA, University of Lleida, 25198 Lleida, Spain.
E-mail address: lorenzo.fraile@ca.udl.cat (L. Fraile).

https://doi.org/10.1016/j.scitotenv.2021.147816

recover, but also the number of people who die from infection, which falls from 0.41% of the population over a 130 day period without protective measures to 0.15, 0.08 and 0.06% if 25, 50 and 75% of the population had been vaccinated in combination with protective measures at the same time, respectively.

1. Introduction

A new coronavirus (SARS-CoV-2) spread quickly in China at the end of 2019, and then rapidly in other areas. The first case of SARS-CoV-2 was reported on 1 December 2019 in the city of Wuhan (China) and the initial outbreak was connected to the Huanan seafood market (Zhang et al., 2020; Mizumoto et al., 2020). This new coronavirus causes a disease named Covid-19 with clinical signs that vary widely between patients, from an asymptomatic infection to severe disease requiring critical care in hospital. Many different symptoms associated with this disease have been described and vary on a patient-to-patient basis. The most common symptoms are cough, fever, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, and diarrhea (Kui et al., 2020; Casas-Rojo et al., 2020). As a result, a percentage of patients finally die as a consequence of the disease. Mortality varies according to country and other factors such as patient age, ethnicity, underlying disease comorbidities, and the measures taken to treat the disease (https://ourworldindata.org/mortality-risk-covid#the-current-case-fatality-rate-of-covid-19).

Europe become a new centre of the outbreak of this new virus during spring 2020, but it became distributed worldwide within a very short period of time from December 2019 to March 2020 (Spiteri et al., 2020; Li et al., 2020). As a consequence of this rapid spread, the World Health Organization (WHO) declared Covid-19 to be a global pandemic. Afterwards, on 17 March 2020, the European Union adopted a decision unprecedented in its history and closed all its external borders in an attempt to mitigate the spread of this global pandemic.

During the first wave of disease, most countries only had the capacity to test a small proportion of suspected cases and diagnostic tests were reserved for severely ill patients or high-risk groups (e.g. those who had had contacts with confirmed cases). A 2–3 week period between infection and the outcome became established in the literature (Lei et al., 2020; Qin et al., 2020). The available data therefore gave a systematically biased view of trends in the pandemic's spread. For this reason, the recorded death records were more informative because they are registered in a more robust way in many countries, although the time lag between the outcomes of treatment and the registration of deaths should be taken into account.

Different research teams have studied the epidemiological parameters of SARS-CoV-2 (Byrne et al., 2020) although many are subject to continuous updates due to the short period of time since the outbreak began (Nishiura, 2007). These parameters are an essential tool in deciphering the most suitable preventive measures to control this disease. Mathematical models can provide new insights into the epidemiology of infectious diseases and suggest criteria for more efficient control strategies. Such models are tools for understanding key points in epidemiology such as disease transmission and dynamics, revealing the implications of the spread of pathogens. Model outcomes for 'what if' scenarios can be used to predict the effects of future interventions. However, most of the models developed so far have low predictive performances because of the uncertainty of some of the epidemiological parameters on which they are based (Huang et al., 2020; Press and Levin, 2020). Thus, ordinary differential equations (ODE), partial derivative equations, real-time estimation of mortality caused by COVID-19 using patient information base algorithm have been used to model the dynamics of SARS-CoV-2 outbreak (Wang et al., 2020). On the other hand, Population Dynamic P system (PDP) models (inspired by the biology of cell function) provide other approach of modelling that have never been applied in human epidemiology until now (Colomer et al., 2021). Briefly, cells can perform multiple processes simultaneously and in a synchronized fashion, which makes them suitable for the modelling of complex problems. New emerging generations of computational models such as PDP models are useful tools for the study of complex problems with very large numbers of interactions in a more efficient way and have been successfully applied in ecology (Margalida et al., 2011; Colomer et al., 2013) and veterinary medicine (Colomer et al., 2019, 2020). These agent-based models do not require a high workload from a computational point of view and can be run on an everyday laptop.

A PDP agent-based stochastic model was developed to decipher the course of the SARS-CoV-2 pandemic under several different epidemiological scenarios. Our first goal was to set up a simulation model, based on PDP model criteria, for any new disease in a naïve population using high-resolution population density data, data on human travel patterns, and average contact frequencies between people. The model was validated using the Spanish outbreak data before and after contact control measures such as social distancing and lockdowns. The second goal was to decipher the effects of a vaccination program with several levels of vaccine efficacy and coverage in the population using the previously developed model.

2. Materials and methods

2.1. Ethical statement

Not necessary because modelling exercises do not involve any experiments, either with animal or human subjects.

2.2. SARS-CoV-2 modelling using a PDP model

PDP models (Păun et al., 2010) are computational models inspired by cell functioning whereby small organelles grow, evolve, reproduce, and die, while interacting with their surroundings and other organelles of the same or different types. Cells evolve in a random way and PDP models emulate their functions through rules of evolution that turn them into stochastic models. The components of a PDP model (Colomer et al., 2013) include: 1) the number of environments; 2) the membrane structure of the cell contained in each environment; 3) the objects in the initial configuration; and 4) the rules of evolution (Fig. 1). Cell membranes have a hierarchical organization, and the outer membrane (skin membrane) may contain more membranes within. To differentiate them, they are labeled with a subscript, the state of the membrane being indicated by a superscript which indicates its electric charge (either +, −, or 0). The objects associated with the individuals in the population reside in the spaces delimited by the membranes. Thus, in our model the object *S* indicates an individual susceptible to infection, *I* indicates an infected individual, while *R* indicates a recovered individual (Fig. 1). The rules of evolution are written in the form of a chemical reaction (Fig. 1): if a healthy individual (*S*) is in contact with an infected one (*I*), it can become infected with a probability *p*. If an infected individual is outside membrane 1 and this membrane also has a positive charge, it can recover with probability *r*.

The model mimics the functioning of a society in a simplified way, so the study area must be divided into differentiated physical units. In the case of Spain, where there are 19 administrative communities, it would be divided into 19 areas where the density of population is assumed to be the same for each region but different across them. In each area, the population is divided into age groups that the investigator can modify

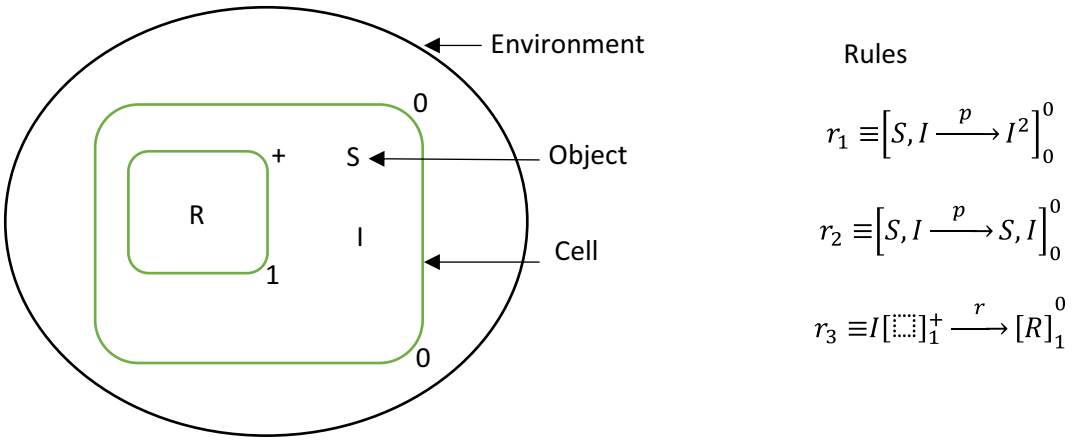


Fig. 1. Components of a PDP model for modelling SARS-CoV-2.

from the input console. In the case of Spain, the population age groups were defined as 0–2 (nursery), 3–5 (preschool), 5–11 (primary education), 12–17 (secondary education), 18–25 (university education), 26–60 (working period) and >60 years old (elderly/retired from work). The retired period was divided into three additional subperiods (61–70, 71–80 and >80 years old) due to the different lethality of the disease observed during the elderly period. Each age group has its own behavior and daily routines, which will determine the average number of people with whom members of the group interact on a daily basis, as well as its movement characteristics between geographical areas. It is assumed that each person inside the same age group has a similar behavior. Thus, the number of contacts is an average value inside each age group. Thus, it was expected that a 10-year-old child was more likely to transmit the virus to children of similar ages than to adults, whereas an older person tends to interact more with older people. In general, a person is more likely to transmit the virus to another person of a similar age group (Fig. 2).

The model defines the average number of people in each age group with a close relationship to people of any other age group. Note that, it is not known how the virus was introduced into the population and that the model makes it possible to choose the number of initial virus foci (index cases) and to place them in a deterministic or random way among the geographical areas that have been established. Because it is not known how the virus was first introduced, the foci were initially distributed at random in all of the simulations. In summary, the model used epidemiological and demographic parameters (Table 1) for simulation (Guan et al., 2020; Lauer et al., 2020; He et al., 2020; Holshue et al., 2020; Chen et al., 2020; Hellewell et al., 2020; Anderson et al., 2020; Bi et al., 2020; Liu et al., 2020a, 2020b; Ferguson et al., 2020). In the case of SARS-CoV-2, the published epidemiological characteristics of the virus were used in the execution of the model (Table 1) in order to predict the dynamics of the virus spread. Remarkably, in this model the reproduction rate was not included as a key parameter to launch the model and the probability of virus transmission from infected people to uninfected ones was only introduced into the model as a variable to find out which value better fitted the predicted outcomes when compared with the real data reported from the Spanish outbreak. Asymptomatic and symptomatic individuals can both transmit the disease, and the contagious period can be modified by the investigator according to updated information regarding the disease as new information comes to light. It was assumed that if an individual was symptomatic, the disease was detected and, consequently, the person was required to self-isolate so as not to infect more people. In the model, it is assumed that the persons respect strictly this recommendation. The values introduced into the model for each parameter were means ± standard deviations. Therefore, the model randomly generates values for incubation time, contagiousness, and the time taken to recover for each infected individual. Once an individual had recovered from the disease, it was assumed that they were immunized for a variable time *t*, measured in days. If people did not manifest the disease, they went on with normal life, implying that they were free to move between communities. The model estimates a probability of travel between or inside each community and also estimates an average duration of each trip, measured in days.

PDPs are agent-based models in which each individual moves around acting according to their own specific rules and is included in larger groups (e.g. communities), in order to better mimic the dynamics of human populations. In our case the number of individuals was 46 million (the population of Spain), grouped into 19 communities. The unit of work time was one day. The model outputs were the number of people in the chosen community, day, and age group that were: asymptomatic; symptomatic; newly infected each day; recovered after infection; and died after infection. Asymptomatic people travelling to other communities and those who were infected during the trip were registered, grouping them by community, day, and age group. All this information is available on a daily basis on the simulation but we have decided to show data in a simpler way. Thus, we have showed the data as dead persons and recovered ones that are the infected ones that have overcome the disease on a daily basis. The model allows the investigator to quantify the movement restrictions necessary to control the pandemic because they can be set up as parameters in the model according to the investigator's requirements. Moreover, the model also allows the investigator to set the percentage compliance with the measures at the individual level in the various age ranges. Finally, the model also allows study of the effect of vaccinating a set percentage of the population with a vaccine of a given efficacy. The vaccine is assumed to be administered randomly in the population without taking into account different age groups. The detailed evolutionary rules of the model are provided in the Supplementary information (see Appendix A).

2.3. SARS-CoV-2 outbreak modelling with and without control measures

PDP models were used to assess the effect of different control measures to mitigate the SARS-CoV-2 pandemic. We simulated the effectiveness of control measures (contact reduction measures, closure of communities (lockdown) and protective measures) and vaccination in controlling the disease under different protective vaccination levels (i.e. efficacy level combined with population coverage). This analysis was performed in three Phases:

2.3.1. Phase 1

The first experiments were performed to estimate the probability of disease transmission, validated against real data from the Spanish

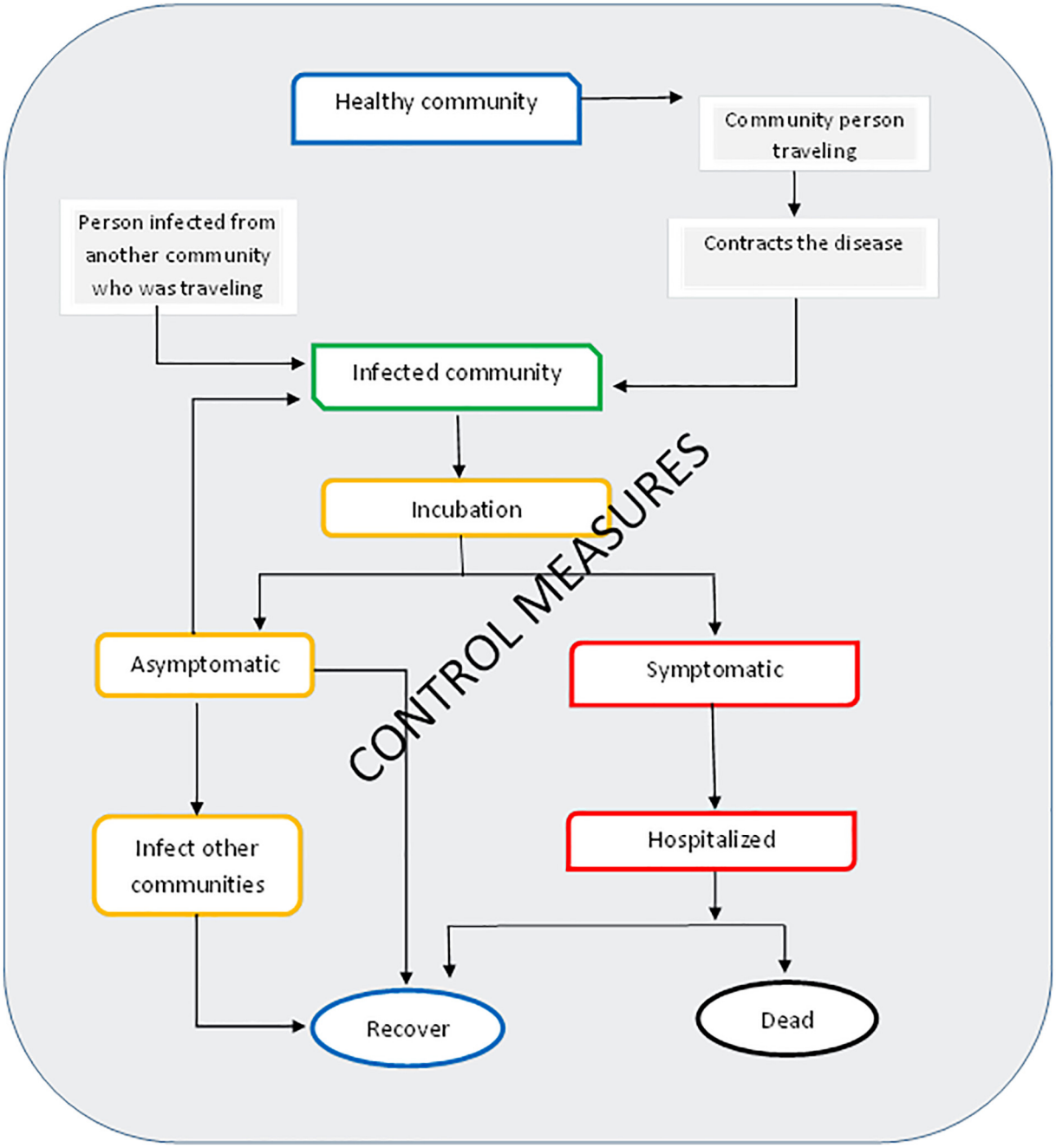


Fig. 2. Flow of SARS-CoV-2 in the population, taking into account the status (infected or non-infected), the development of symptoms (asymptomatic or symptomatic), the location in any geopraphical community, and the necessity for hospitalization of individuals.

outbreak, using death toll as the key parameter. Seven experiments were performed using a probability of transmission in the range 0.05–0.5. The dynamics of the disease were simulated over a 90 day period with 30 repetitions of each scenario.

Modelling SARS-CoV-2 is complex and depends on various parameters. The sensitivity of the model can be studied with respect to each parameter but here we focus on only several epidemiological parameters pertinent to the objectives of this study, and held the remainder of the parameters constant in the model runs (Table 1). The sensitivity of the PDP SARS-CoV-2 model was studied using a Box-Behnken design with three factors, each at two levels: the contagious period (7 and 15 days); the number of foci at the beginning of the outbreak (1 and 15); and the probability of transmitting the virus from an infected to a non-infected person ($p = 0.05$ and 0.15). Sixteen scenarios were therefore modelled.

Two response surfaces were estimated, one for each of the response variables studied: the numbers of people who died and who recovered following infection (the total number of people infected is the sum of those recovering and dying). These surfaces allowed us to assess the sensitivity of the PDP model to small variations in the factors involved.

2.3.2. Phase 2

Contact reduction measures, closure of communities (lockdown), and protective measures (including facing mask wearing, social distancing, and hand hygiene) were studied as pandemic control measures. The first two factors were studied at two levels: Yes/No. Contact reduction measures can be applied at different levels (defined in Table 1 as the r parameter). In this Phase, contact reduction measures mean complete removal of contacts between age

groups, with the exception of individuals between 18 and 70-years-old, where the reduced contact taken to be 80% with a 90% compliance. In addition, the simulations of contact reduction measures began 21 days after the beginning of the outbreak and ended on day 63, and the closure of communities (lockdown) ran from day 20 to day 48 following the beginning of the outbreak. Protective measures are designed to decrease the probability of virus transmission from infected to non-infected people. The starting point was a transmission probability of 10% and this value could be reduced depending on the measures applied and the degree of compliance. The range of values studied therefore went from 1% to 10%.

Our study showed that control measures significantly affect the outcomes of the model: the numbers of people dying and recovering. The factors studied and the levels used are shown in Table 2. The remainder of the parameters used in the model are shown in Table 1.

2.3.3. Phase 3

The effect of protecting part of the population by applying protective measures and mass vaccination was modelled over a 130 day period. The probability of disease transmission without and with protective measures was set at 10% (initially validated in Phase 1 of the study) and 5%, respectively. The percentage of the population protected by vaccination was set as either 0 (no vaccination), 25, 50 and 75%, taking into account the combination of vaccine efficacy and population coverage (see Section 2.4 below). A total of 30 repetitions of the eight scenarios were performed in these experiments.

2.4. Data analysis

All statistical analyses were performed using the R Core package (R Core, 2020, https://www.R-project.org/). The EpiEstim package was used to calculate the reproduction rate taking into account the outcome

Table 1
Epidemiological and demographic parameters used in the SARS-CoV-2 PDP model.

Epidemiological parameter	Value	Definition	References
g_2	5.1±10%	Average duration of the virus incubation (days).	Lauer et al., 2020, He et al., 2020, Holshue et al., 2020
g_3	14±10%	Average duration of virus transmissibility (days).	Holshue et al., 2020, Chen et al., 2020; Hellewell et al., 2020, Anderson et al., 2020, Bi et al., 2020
g_4	21±10%	Average time needed to recover from the disease (days)	Lauer et al., 2020, He et al., 2020, Holshue et al., 2020
p_i	Variable, but the same value has been used for all age groups in the different scenarios.	Probability that a person, belonging to age group i ($1 \leq i \leq 9$), has contact with an infected person, and becomes infected.	
$Sint_i$	Age group / Probability 0–2 / 0.01 3–5 / 0.01 6–11 / 0.03 12–18 / 0.05 19–25 / 0.1 26–60 / 0.15 61–70 / 0.185 70–80 / 0.185 >80 / 0.185	Probability that an infected person of age group i ($1 \leq i \leq 9$) will require medical treatment.	He et al., 2020, Ferguson et al., 2020
pd_i	Age group / Probability 0–2 / 0.003 3–5 / 0.003 6–11 / 0.003 12–18 / 0.001 19–25 / 0.003 26–60 / 0.01 61–70 / 0.044 70–80 / 0.138 >80 / 0.25	Probability that a person of age group i ($1 \leq i \leq 9$) will die after being infected.	He et al., 2020, Ferguson et al., 2020

Demographic parameter	Definition	References
$q_{c,i}$	Number of people in the community c $(1 \leq c \leq Comunity)$ who belong to age class i $(1 \leq i \leq 9)$.	INE. Instituto Nacional de Estadística (INE), Spain, 2020. https://www.ine.es/
$Focus$	Number of people infected at the initial stage of the pandemic (required parameter if the outbreaks of infection are random).	Model option.
$qf_{c,i}$	Number of people infected, at time 0, in the community c $(1 \leq c \leq Comunity)$ who belong to age group i $(1 \leq i \leq 9)$ (required parameter if the foci of infection are not random).	Model option.
$People_{i,j,r}$	Number of people of age group $j(1 \leq j \leq 9)$ who are in contact with people of age group i $(1 \leq i \leq 9)$, applying measures of r type $(1 \leq r \leq 4)$. The model allows the application of four types of measure that involve different contacts between groups of people. The case $r = 1$ corresponds to contacts assuming free movement in the population (previous to the pandemic), The investigator can define different measures of decreasing number of contacts by age group. The greater the number, the stricter are the measures required to decrease the contacts (r) $from$ 2 to 4.	Model option.
$Aply_{r,i}$	Percentage of people of age group i $(1 \leq i \leq 9)$ complying with the contact reduction measure r $(1 \leq r \leq 4)$.	Model option.
pty_i	Probability that a person of age group i $(1 \leq i \leq 9)$ travels to another community on a particular day. The same value used was (0.0005).	Model option. The probabilities were estimated based on INE information, Spain 2020.
$TimeT_i$	Average duration (days) of a trip to another community of an age class i $(1 \leq i \leq 9)$. 2 if $i \leq 25$ and 1 if $i >$ 25.	Model option. The durations used were estimated based on INE information, Spain 2020.
$pt_{c1,c2}$	Probability that a person who has travelled goes from community c_1 to community c_2 $1 \leq c1, c2 \leq Comunity$.	Model option. The probabilities used were estimated based on INE information, Spain 2020.

of the model. This package includes tools to quantify transmissibility throughout a pandemic using the analysis of time series of incidence as described in Cori et al. (2013) and Wallinga and Teunis (2004).

Box-Bhenken designs were performed to find out the sensitivity of the model using the DoEbase package in the R software package. Two response surfaces were obtained, one for each dependent variable, and these were used to estimate the sensitivity of the model. In Phase 1 of the study, a relative mistake was calculated from the difference between the values obtained by the model and the actual values, as published by the Spanish Ministry of Health, according to formula (1). The probability of transmission of the disease that generates the minimum relative mistake was chosen as the most suitable one to set up the model, assuming that the virus circulates freely in the population without control measures.

$$Relative\ Mistake = \frac{Model\ value - Governmental\ value}{Governmental\ value} \cdot 100 \quad (1)$$

The results obtained in Phase 2 and Phase 3 were analyzed using a generalized linear model (GLM), with a link identity function and a Gaussian distribution. For Phase 2, the independent variables were contact reduction measures, closure of communities (lockdown) and protective measures. For Phase 3 of the study, the independent variables were the percentage of the population protected by vaccination, calculated as the percentage of people vaccinated (coverage) multiplied by the efficacy of the vaccine, and the application of social measures. The response variables in all of the Phases correspond to the numbers of people dying and recovering after infection with SARS-CoV-2. The effects were considered to be significant when $p < 0.05$.

Table 2
Levels of the factors under study.

Factor	Levels
Contact reduction measures	Yes/no
Closure of communities (lockdown)	Yes/no
Probability of transmitting the disease from an infected to an uninfected person applying different protective measures	[0.01 − 0.1]

3. Results

3.1. Phase 1

3.1.1. Model validation

Model validation was performed taking into account the official death toll values as a key parameter due to its robustness. Where the probability of transmission is 0.05 or 0.15, the model underestimates and overestimates the official data, respectively, assuming free circulation of the virus in the population, the differences being always negative or positive, respectively (Table 3). Where $p = 0.1$, the differences between the values estimated by the model and the official data can be positive or negative and the mean relative error was the smallest of the three values of probability tested, suggesting that a probability of disease transmission of around 0.10 was probably closest to reality (Table 3). Therefore, it appears that the outcomes generated when the p value = 0.10 are very close (Fig. 3) to the actual underlying reproduction ratio (Rt) observed during the outbreak, as published by the Spanish Department of Health (90-day series from 25 February to 24 May) (Fig. 3).

Table 3
Results of the validation tests of the PDP SARS-CoV-2 model showing the range of values (minimum and maximum), how many differences were positive or negative, the mean value of the errors, and the mean value of the absolute value of the errors.

Probability of transmitting the disease from an infected to an uninfected person assuming free circulation of the virus in the population	0.05	0.1	0.15
Minimum relative error	−0.99	−0.81	0.00
Maximum relative error	−0.57	0.25	2.19
Negative relative errors	74	25	0
Positive relative errors	0	49	73
Mean relative error	−0.86	−0.10	0.94
Mean absolute relative error	0.86	0.25	0.94

Table 4
Results of the Box-Behnken model to study the sensitivity of the PDP COVID-19 model.

Box-Behnken result	Dead people		Recovered people	
	Value	P-val	Value	P-val
(Intercept)	**186,753.3**	**<0.001**	**25,839,046.5**	**<0.001**
Contagious period	60.8	0.68	**−63,596.1**	**<0.001**
Number of foci	164.5	0.28	−2100.5	0.70
Probability of transmission	**57,799**	**<0.001**	**8,004,546.4**	**<0.001**
Contagious period: number of foci	14.5	0.94	−1785.5	0.81
Contagious period: probability of transmission	242	0.27	11,082.8	0.18
Number of foci: probability of transmission	73.5	0.72	−720.5	0.92
Contagious period^2	63.6	0.76	−8292.9	0.30
Number of foci^2	−129.9	0.54	6126.9	0.43
Probability of transmission^2	**−14,053.4**	**<0.001**	**−1,984,689.4**	**<0.001**

3.1.2. Uncertainty and sensitivity analysis results

The sensitivity of the model was assessed using a Box-Behnken design. Variations in the outcome of the model were studied depending on the number of foci, the probability of transmission of the disease, and the duration of the contagious period. The two response surfaces are detailed in Table 4.

The two outcome variables (dead and recovered people) were significantly sensitive to variations in the probability of transmission of the disease ($p < 0.05$). Thus, a 1% increase in the probability of transmission resulted in a 0.03% increase (11,560 people) and 3.48% increase (1,600,909 people) in the number of people who died and recovered in the Spanish population, respectively (Table 5). However, the only outcome variable that was significantly sensitive to variations in the contagious period was the number of people who recovered, but the effect of changing this variable by 1% was less than the effect due

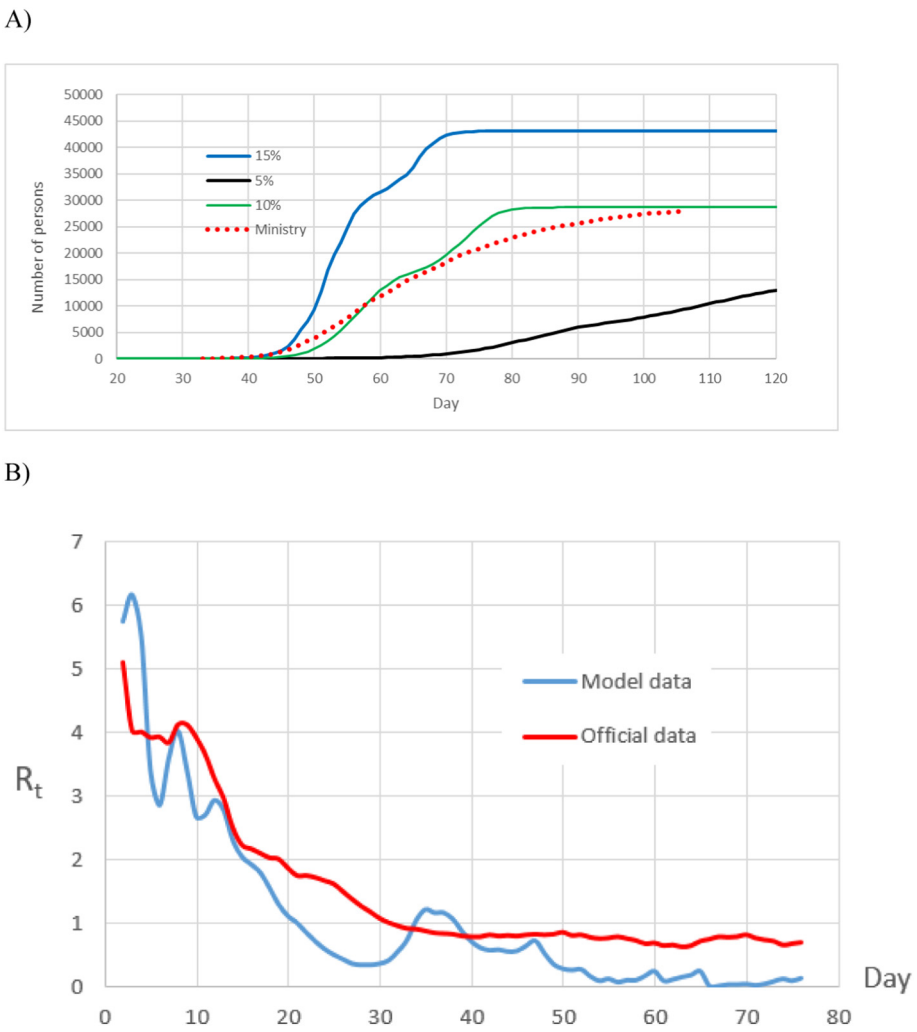


Fig. 3. A) Number of deaths depending on the probability of transmission used for modelling and the official data from the Spanish Department of Health. B) Effective reproduction number (Rt) calculated from the data obtained from the model, in the case of a 10% probability of transmission of the disease from infected to non-infected people, and the figures published by the Spanish Department of Health (from 25 February 2020 to 24 May 2020, a 90-day series) using the EpiEstim package as described in Cori et al. (2013) and Wallinga and Teunis (2004). Blue line: model data; red line: official data. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Effect of an increase of 1% in the independent variables on the outcome of the model.

Sensitivity	Dead people		Recovered people	
	Absolute	Relative[a]	Absolute	Relative[a]
Number of foci	23.5	0.00%	−300.07	0.00%
Probability of transmission	11,559.8	0.03%	1,600,909.28	3.48%
Contagious period	15.2	0.00%	−15,899.025	−0.03%

[a] The relative value was calculated with respect to the total population, 46,014,554.

Table 6
GLM model results to study the effects of contact reduction measures, closure of communities, and protective measures. Statistically significant results are shown in bold type.

		Closure of a community (lockdown)	Contact reduction measures	Protective measures
Dead people	Coefficient	−4.81	238.88	287,909.44
$D^2 = 99.9$	P value	0.531	0.123	**<0.001**
Recovered people	Coefficient	−6454	−136,221	46,214,699
$D^2 = 98.9$	P value	0.431	0.406	**<0.001**

Table 7
Percentage of individuals with respect to the total population (46,014,554 people) as a function of the % of the vaccinated population, and the probability of disease transmission with and without social measures.

Probability of disease transmission (%)	5 (with social measures)				10 (without social measures)			
Population protected by vaccination (%)	0	25	50	75	0	25	50	75
Recovered (%)	34.09	25.54	12.06	7.95	56.08	41.69	27.68	13.18
Dead (%)	0.25	0.15	0.08	0.06	0.41	0.25	0.14	0.10

to the probability of transmission (Table 5). Finally, the two outcome variables were not significantly affected by variations in the number of foci at the beginning of the outbreak ($p > 0.05$).

3.2. Phase 2

3.2.1. Contact reduction, the closure of communities and protective measures

In Phase two, the effect of contact reduction measures, closure of communities (lockdown) and protective measures (including face mask wearing, social distancing and hand hygiene) were studied as pandemic control measures, as detailed in the Materials and methods section. Protective measures significantly affected the two outcome variables in the long term (Table 6). The closure of communities and contact reduction measures did not significantly affect the response variables in the long term. It was not observed any significant interaction ($p > 0.05$) in the GLM.

3.2.2. Trend of SARS-CoV-2 outbreak with vaccination and the application of protective measures in the population

The effects of vaccinating 25, 50 and 75% of the population, both without or with the application of additional control measures were modelled (Table 7; Fig. 4). We also modelled the number of people who died and recovered when the probability of transmission was set to 0.1 (Phase 1 of this study) both without the application of protective measures and with these measures in place (probability of transmission of 0.05). In general terms, the best results (higher percentage of reduction in all the outcome variables) were observed when the vaccine was administered to a larger part of the population (75%), both without and with the application of protective measures. With this level of vaccine protection, the effect of protective measures on the final outcome of the pandemic was the least. However, the results of the outcome variables were clearly improved by protective measures at the intermediate level (50%) of population vaccination. Moreover, the largest reduction in the percentage of people who died and recovered was observed when 25 and 50% of the population was vaccinated in combination with the application of protective measures versus vaccination without the application of protective measures (Table 7; Fig. 4). It was not observed any significant interaction ($p > 0.05$) in the GLM.

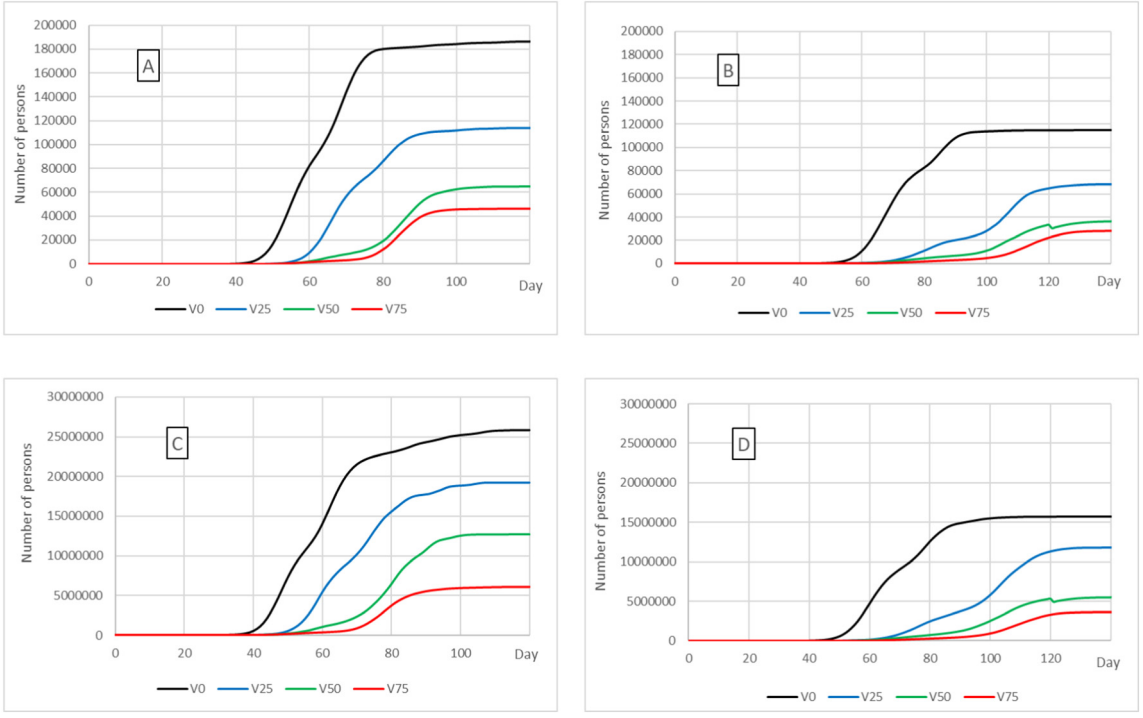


Fig. 4. Graphs A and B show the progress of the death toll depending on the percentage of the population protected by vaccination (from 0% (V0) to 75% (V75)), without and with the application of protective measures, respectively. Graphs C and D show the number of people who recovered depending on the percentage of the population protected by vaccination (from 0% (V0) to 75% (V75)), without and with the application of protective measures, respectively.

4. Discussion

The recent recurrent global pandemic events in which virus dissemination is not easily controlled have provoked social alarm among health administrations resulting in significant social and economic impacts (Yue et al., 2021). Epidemiological modelling is the most commonly used means of providing data to help policy-makers anticipate and design the best management strategies to control any outbreak. However, the difficulties of predicting the course of a pandemic like the current one operate at three levels: the quality of the data; the suitability of the epidemiological models; and the intrinsic uncertainty of the epidemiological models (Yue et al., 2021; Poletto et al., 2020). At the beginning of this pandemic, many epidemiological models were used, such as SIR and its variants (SEIR, SITR, SIRS, SEQJR), that are based on differential equations (IHME COVID-19 Forecasting Team; Al-Anzi et al., 2020; Barbarossa et al., 2020; Goscé et al., 2020). These models have their limitations in addressing complex problems for a new disease where some of the key parameters are unknown and are difficult to apply to a population where urgent measures are required to control the outbreak. Therefore, the control measures that they recommend require modifying the basic epidemiological parameters for any disease (IHME COVID-19 Forecasting Team; Goscé et al., 2020; Adiga et al., 2020; Ortega et al., 2020; Tang and Wang, 2020). As a consequence, there are many epidemiological models for COVID-19 in the literature with a variety of conflicting predictions. Therefore, the Center for Disease Control present these individual predictions for each model alongside an "average" prediction taking account of all the models together (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/forecasting-us.html).

In this paper, we propose a new computational model for COVID-19 (the PDP COVID-19 model). This kind of model has not higher computational costs but allows the study of complex problems in parallel, with many interactions between them at individual level. PDPs are relatively new models which have been successfully applied to the study of complex ecosystems (Colomer et al., 2014) and for veterinary diseases (Colomer et al., 2019, 2020). They allow the generation of a daily photograph of all the individuals in the population, so it is possible to estimate the number of people who are infected whether symptomatic, asymptomatic, hospitalized, incubating the disease, or transmitting the disease to other communities/people. Some of these outputs allow evaluation of the dynamics of the pandemic while others can be used to estimate the healthcare and financial resources that will be needed. The PDP model uses epidemiological data for the disease (Table 1) but is flexible enough to determine the basic reproduction ratio (R_o), the critical parameter for understanding the transmission of a disease at the population level. R_o is an input parameter in many previously published COVID-19 models (Liu et al., 2020a, 2020b; Yue et al., 2020). However, in our model R_o does not need to be obtained from the literature to set up the PDP model. It can be obtained as an outcome from the model after setting different probabilities of transmission and checking the model prediction against actual infection data. This characteristic of the model allows the R_o to be constantly checked as the outcomes of various control measures are applied, something not possible with other models [37–40]. Moreover, the sensitivity of the model can be assessed using a Box-Behnken design. Variations in the outcome of the model were studied depending on the number of initial foci, the probability of transmission of the disease, and the duration of the contagious period. The sensitivity of the model was demonstrated for changes in the probability of transmission of the disease, contagious period, and the resulting numbers of people who died or recovered. In this way, the model can be used to analyse the relative efficacy of different control measures. Finally, because PDP models are modular, they allow the incorporation of new components as new knowledge accumulates, especially important in the case of SARS-CoV-2 as the pandemic parameters change and unfold. However, our PDP model has also limitations. Thus, it was not considered potential changes to the virus transmissibility due to environmental factors such as temperature and humidity. Moreover, the transmission among members of the same family is partially captured in the model but it was not explicitly taking into account the effect of transmission inside the family. Finally, our model did not also consider the effect of different population density inside the communities (Wong and Li, 2020) nor the reintroduction of SARS-CoV-2 into the population by infected travellers from other countries. In connection with the control measures, the model assumes that the vaccination is applied randomly in the population without taking into account age groups. However, governments are focusing the vaccination in high-risk groups to decrease the hospitalizations and lethality in the population. Thus, the output of our model can be considered a worst-case scenario in relation with the outcome due to vaccination. Accordingly, our model is probably underestimating the positive effects of the vaccination at population level compared with an age-driven vaccination approach. While our results probably do not agree exactly with reality due to the former reasons, they do serve as useful comparisons of the likely outcomes in the presence of various control measures. For this reason, we performed extensive sensitivity analyses which show that the modelling results presented here are robust within the plausible range of parameter values for the course of the COVID-19 pandemic in Spain. In conclusion, the differences described from the different interventions in the model are quite robust in relative terms but the absolute values must be interpreted with caution because they are depending on the parameters used to run this model plus the intrinsic limitations that any model has to mimic reality.

Model validation was performed taking into account the official Spanish death toll figures as the most robust key parameter. A probability of transmission of 0.10 allows the prediction of data very close to the real figures observed during the outbreak (Fig. 3) and was set as our baseline level for the course of the pandemic without control measures. Moreover, the R_o obtained from the model was also very close to the data published by the Spanish Department of Health (Fig. 3). These results allowed us to confirm that the model was good enough to predict the COVID-19 pandemic, at least in Spain. Our model must be checked against the data from other countries if it is to be used worldwide. In any case, our experience with the model in comparing different interventions to control the disease leads us to believe that the results can be extrapolated to any other country.

The number of initial outbreaks and the contagious period are not significant factors in determining the course of the COVID-19 pandemic, probably due to the exponential spread of the disease (Sanche et al., 2020). It is clear that lockdown and contact reduction measures are effective in controlling the COVID-19 pandemic in the short term (Kissler et al., 2020). They have been widely applied in many countries as frontline measures to avoid the collapse of national health systems but our model foresees that these measures are not effective in controlling the COVID-19 pandemic over the longer term because the initial course of the disease has continued after the measures were lifted (Davies et al., 2021; Li et al., 2021). However, our study concludes that reducing the probability of transmission of the disease is a useful measure that does reduce its spread over the long term. Unfortunately, measures such as social distancing, hand hygiene and wearing face masks are difficult for populations to accept over the long-term. Moreover, they are only efficacious when population compliance is very high, and compliance can be very variable across countries.

In this paper, we studied the effect of combining vaccination with the application of protective measures to control the course of the COVID-19 pandemic. It seems unnecessary to check the combination of both measures because of the high percentage reduction in the number of people who die or recover after infection when a large proportion of the population (75%) is protected with the vaccine, both without and with the application of protective measures. Therefore, if this level of vaccine protection could be achieved, the extra effect of protective measures on the final outcome of the pandemic would be minimal. However, the actual efficacy of the various COVID-19 vaccines is

currently unknown, although the data supplied by pharmaceutical companies seems extraordinary (>90%) (Polack et al., 2020; Knoll and Wonodi, 2020). In any case, the availability of the vaccine will be very low at first, although supplies should increase during 2021. It will therefore be necessary to combine protective measures and vaccination for a long time until high vaccination levels can be achieved. The results of the outcome variables are clearly improved by protective measures at intermediate population vaccination levels (25–50%). Therefore, the largest variation in the percentage of people who die and recover was observed when 25–50% of the population was protected by vaccination in combination with protective measures compared with 25–50% vaccination and no protective measures. Finally, the effect of cost-effective plan for global testing has not been addressed in this work but we have also analyzed this control measure in a recent paper (Colomer et al., 2021) where results clearly support the value of contact tracing as an effective tool in controlling the course of the pandemic, in common with other published studies (Aleta et al., 2020; Li and Giabbanelli, 2020) even with a low (40%), but realistic level of contact tracing. The problem with this measure is that it requires a large number of tests with a high cost for governments.

In summary, lockdowns and contact reduction measures only delay the spread of the SARS-CoV-2 virus in the population because it resumes its previous dynamics as soon as the restrictions are lifted. Accordingly, the best approach would be to combine protective measures and vaccination to reduce both the number of people who die and recover after infection.

CRediT authorship contribution statement

Conceptualization, M.A.C., A.M. and L.F.; formal analysis, M.A.C.; investigation, L.F.; methodology, M.A.C. and L.F.; writing—original draft, M.A.C., A.M. and L.F.; writing—review and editing, M.A.C., A.M., F.A., A.V. L.F. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare no competing interest.

Acknowledgements

This study was partially funded by the University of Lleida (UdL). The comments of four anonymous reviewers improved a previous version of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.147816.

References

Adiga, A., Dubhashi, D., Lewis, B., Marathe, M., Venkatramanan, S., Vullikanti, A., 2020. Mathematical models for COVID-19 pandemic: a comparative analysis. J. Indian Inst. Sci. 100, 793–807.

Al-Anzi, B.S., Alenizi, M., Dallal, J.A., Abookleesh, F.H., Ullah, A., 2020. An overview of the world current and future assessment of novel COVID-19 trajectory, impact, and potential preventive strategies at healthcare settings. Int. J. Environ. Res. Public Health 17, 7016.

Aleta, A., Martín-Corral, D., Pastore y Pionti, A., Ajelli, M., Litvinova, M., Chinazzi, M., Dean, N.E., Halloran, M.E., Longinig, I.M.Jr., Merler, S., Pentland, A., Vespignani, A., Moro, E., Moreno, Y. 2020. Modelling the impact of testing, contact tracing and household quarantine on second waves of COVID-19. Nat. Hum. Behav., 4, 964–971.

Anderson, R.M., Heesterbeek, H., Klinkenberg, D., Hollingsworth, T.D., 2020. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet 395, 931–934.

Barbarossa, M.V., Fuhrmann, J., Meinke, J.H., Krieg, S., Varma, V., Castelletti, N., 2020. Modeling the spread of COVID-19 in Germany: early assessment and possible scenarios. PLoS One 15, e0238559.

Bi, Q., Wu, Y., Mei, S., Ye, C., Zou, X., Zhang, Z., Liu, X., Wei, L., Truelove, S.A., Zhang, T., Gao, W., Cheng, C., Tang, X., Wu, X., Wu, Y., Sun, B., Huang, S., Sun, Y., Zhang, J., Ma, T., Lessler, J., Feng, T., 2020. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect. Dis. 20, 911–919.

Byrne, A.W., McEvoy, D., Collins, A.B., Hunt, K., Casey, M., Barber, A., Butler, F., Griffin, J., Lane, E.A., McAloon, C., O'Brien, K., Wall, P., Walsh, K.A., More, S.J., 2020. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. BMJ Open 10, e039856.

Casas-Rojo, J.M., Antón-Santos, J.M., Millán-Núñez-Cortés, J., Lumbreras-Bermejo, C., Ramos-Rincón, J.M., Roy-Vallejo, E., Artero-Mora, A., Arnalich-Fernández, F., García-Bruñén, J.M., Vargas-Nuñez, J.A., 2020. Características clínicas de los pacientes hospitalizados con COVID-19 en España: resultados del Registro SEMI-COVID-19. Rev. Clin. Esp. 220, 480–494.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395, 507–513.

Colomer, M.À., Margalida, A., Pérez-Jimenez, M.J., 2013. Population dynamics P system (PDP) models: a standardized protocol for describing and applying novel bio-inspired computing tools. PLoS One 8, e60698.

Colomer, M.A., Margalida, A., Palau, A., Valencia, L., 2014. Application of a computational model to assess the population dynamics of zebra mussel (*Dreissena polymorpha*): implications to manage invasive species. Ecol. Complex. 20, 116–126.

Colomer, M.À., Margalida, A., Fraile, L.J., 2019. Improving the management procedures in farms infected with the porcine reproductive and respiratory syndrome virus using PDP models. Sci. Rep. 9, 9959.

Colomer, M.À., Margalida, A., Fraile, L.J., 2020. Vaccination is a suitable tool in the control of Aujeszky's disease outbreaks in pigs using a population dynamics P systems model. Animals 10, 909.

Colomer, M.A., Margalida, A., Alòs, F., Oliva-Vidal, P., Vilella, A., Fraile, L., 2021. Modeling of vaccination and contact tracing as tools to control the COVID-19 outbreak in Spain. Vaccines 9, 386.

Cori, A., Ferguson, N.M., Fraser, C., Cauchemez, S. 2013. New framework and software to estimate time-varying reproduction numbers during epidemics. Am. J. Epidemiol. 178, 1505–1512.

Davies, N.G., Barnard, R.C., Jarvis, C.I., Russell, T.W., Semple, M.G., Jit, M., Edmunds, W.J., 2021. Association of tiered restrictions and a second lockdown with COVID-19 deaths and hospital admissions in England: a modelling study. Lancet Infect. Dis. 21, 482–492.

Ferguson, M., Laydon, D., Nedjati-Gilani, G., Imai, N., Ainslie, K., Baguelin, M., Bhatia, S., Boonyasiri, A., Cucunubá, Z., Cuomo-Dannenburg, G., Dighe, A., Dorigatti, I., Fu, H., Gaythorpe, K., Green, W., Hamlet, A., Hinsley, W., Okell, L.C., van Elsland, S., Thompson, H., Verity, R., Volz, E., Wan, H., Wang, Y., Walker, P.G.T., Walters, C., Winskill, P., Whittaker, C., Donnelly, C.A., Riley, S., Ghani, A.C. 2020 Report 9: impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf. [accessed May 30, 2020].

Goscé, L., Phillips, A., Spinola, P., Gupta, R., Abubakar, I., 2020. Modelling SARS-CoV-2 spread in London: approaches to lift the lockdown. J. Inf. Secur. 81, 260–265.

Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D.S.C., Du, B., Li, L., Zeng, G., Yuen, K.-Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., Li, S., Wang, J.L., Liang, Z., Peng, Y., Wei, L., Liu, Y., Hu, Y., Peng, P., Wang, J., Liu, J., Chen, Z., Li, G., Zheng, Z., Qiu, S., Luo, J., Ye, C., Zhu, S., Zhong, N., 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382, 1708–1720.

He, X., Lau, E.H.Y., Wu, P., Deng, X., Wang, J., Hao, X., Lau, Y.C., Wong, J.Y., Guan, Y., Tan, X., Mo, X., Chen, Y., Liao, B., Chen, W., Hu, F., Zhang, Q., Zhong, M., Wu, Y., Zhao, L., Zhang, F., Cowling, B.J., Leung, G.M., 2020. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat. Med. 26, 672–675.

Hellewell, J., Abbott, S., Gimma, A., Bosse, N.I., Jarvis, C.I., Russell, T.W., Munday, J.D., Kucharski, A.J., Edmunds, W.J., Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Funk, S., Eggo, R.M. 2020. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob. Health 8, e488-e496.

Holshue, M.L., DeBolt, C., Lindquist, S., Spitters, C., Ericson, K., Wikerson, S., Tural, A., Diaz, G., Cohn, A., Fox, L.A., Patel, A., Gerber, S.I., Kim, L., Tong, S., Lu, X., Lindstrom, S., Pallansch, M.A., Weldon, W.C., Biggs, H.M., Uyeki, T.M., Pillai, S.K., 2020. First case of 2019 novel coronavirus in the United States. N. Engl. J. Med. 382, 929–936.

Huang, J., Zhang, L., Liu, X., Wei, Y., Liu, C., Lian, X., Huang, Z., Chou, J., Liu, X., Li, X., Yang, K., Wang, J., Liang, H., Gu, Q., Du, P., Zhang, T., 2020. Global prediction system for COVID-19 pandemic. Sci. Bull. 65, 1884–1887.

IHME COVID-19 Forecasting Team, 2021. Modeling COVID-19 scenarios for the United States. Nat. Med. 27, 94–105.

Kissler, S.M., Tedijanto, C., Goldstein, E., Grad, Y.H., Lipsitch, M., 2020. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 368, 860–868.

Knoll, M.D., Wonodi, C., 2020. Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet 397, 72–74.

Kui, L., Fang, Y., Deng, Y., Liu, W., Wang, M.-F., Jing-PÑing, M., Wei, X., Ying-Nan, W., Min-Hua, Z., Cheng-Hong, L., 2020. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin. Med. J. 133, 1025–1031.

Lauer, S.A., Grantz, K.H., Bi, Q., Jones, F.K., Zheng, Q., Meredith, H.R., Azman, A.S., Reich, N.G., Lessler, J., 2020. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann. Intern. Med. 172, 577–582.

Lei, S., Jiang, F., Su, W., Chen, C., Chen, J., Mei, W., Zhan, L.-Y., Jia, Y., Zhang, L., Liu, D., Xia, Z.-Y., Xia, Z., 2020. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClin. Med. 21, 100331.

Li, J., Giabbanelli, P.J. 2020. Identifying synergistic interventions to address COVID-19 using a large scale agent-based model. medRxiv doi: https://doi.org/10.1101/2020.12.11.20247825.

Li, R., Pei, S., Chen, B., Song, Y., Zhang, T., Yang, W., Shaman, J., 2020. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science 368, 489–493.

Li, Y., Campbell, H., Kulkarni, D., Harpur, A., Nundy, M., Wang, X., 2021. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (*R*) of SARS-CoV-2: a modelling study across 131 countries. Lancet Infect. Dis. 21, 193–202.

Liu, Y., Gayle, A.A., Wilder-Smith, A., Rocklöv, J. 2020a. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J. Travel Med. 27: taaa021.

Liu, Y., Yan, L.M., Wan, L., Xiang, T.-X., Le, A., Liu, J.-M., Peiris, M., Poon, L.L.M., Zhang, W., 2020b. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect. Dis. 20, 656–657.

Margalida, A., Colomer, M.À., Sanuy, D., 2011. Can wild ungulate carcasses provide enough biomass to maintain avian scavenger populations? An empirical assessment using a bio-inspired computational model. PLoS One 6, e20248.

Mizumoto, K., Kagaya, K., Chowell, G., 2020. Effect of a wet market on coronavirus disease (COVID-19) transmission dynamics in China, 2019–2020. Int. J. Infect. Dis. 97, 96–101.

Nishiura, H., 2007. Time variations in the transmissibility of pandemic influenza in Prussia, Germany, from 1918–19. Theor. Biol. Med. Model. 4, 20.

Ortega, D., Kanjo, E., Pogrebna, G., Kaiwartya, O., Johnson, S.D., Hunt, J.A., 2020. A COVID-19-based modified epidemiological model and technological approaches to help vulnerable individuals emerge from the lockdown in the UK. Sensors 20, 4967.

Păun, G., Rozenberg, G., Salomaa, A. (Eds.), 2010. The Oxford Handbook of Membrane Computing. Oxford University Press, Oxford.

Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck, R.W., Hammitt, L.L., Türeci, Ö., Nell, H., Schaefer, A., Ünal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Sahing, U., Jansen, K.U., Gruber, W.C., 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med. 383, 2603–2615.

Poletto, C., Scarpino, S.V., Volz, E.M., 2020. Applications of predictive modelling early in the COVID-19 epidemic. Lancet Digit. Health 2, e498–e499.

Press, W.H., Levin, R.C., 2020. Modeling, post COVID-19. Science 370, 1015.

Qin, J., You, C., Lin, Q., Hu, T., Yu, S., Zhou, X-H. 2020. Estimation of incubation period distribution of COVID-19 using disease onset forward time: a novel cross-sectional and forward follow-up study. Sci. Adv. 6, eabc1202.

R Core Team, 2020. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria URL. http://www.R-project.org/.

Sanche, S., Lin, Y., Xu, C., Romero-Severson, E., Hengartner, N., Ke, R., 2020. High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg. Infect. Dis. 26, 1470–1477.

Spiteri, G., Fielding, J., Diercke, M., Campese, C., Enouf, V., Gaymard, A., Bella, A., Sognamiglio, P., Sierra Moros, M.J., Nicolau Riutort, A., Demina, Y.V., Mathieu, R., Broas, M., Bengnér, M., Buda, S., Schilling, J., Filleul, L., Lepoutre, A., Saura, C., Mailles, A., Levy-Bruhl, D.L., Coignard, B., Bernard-Stoecklin, S., Behillil, S., van der Werf, S., Valette, M., Lina, B., Riccardo, B., Nicastri, E., Casas, I., Larrauri, A., Salom Castell, M., Pozo, F., Maksyutov, R., Martin, C., Van Ranst, M., Bossuyt, N., Siira, L., Sane, J., Tegmark-Wisell, K., Palmérus, M., Broberg, E.K., Beauté, J., Jorgensen, P., Bundle, N., Pereyaslov, D., Adlhoch, C., Pukkila, J., Pebody, R., Olsen, S., Ciancio, B.C., 2020. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Euro Surveill. 25, 2000178.

Tang, Y., Wang, S., 2020. Mathematic modeling of COVID-19 in the United States. Emerg. Microbes Infect. 9, 827–829.

Wallinga, J., Teunis, P., 2004. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am. J. Epidemiol. 160, 509–516.

Wang, L., Li, J., Guo, S., Xie, N., Yao, L., Cao, Y., Day, S.W., Howard, S.C., Graff, J.C., Gu, T., Ji, J., Gu, W., Sun, D., 2020. Real-time estimation and prediction of mortality caused by COVID-19 with patient information based algorithm. Sci. Total Environ. 727, 138394.

Wong, D.W.S, Li, Y., 2020. Spreading of COVID-19: Density matters. PLoS ONE 15 (12), e0242398.

Yue, T., Fan, Z., Fan, B., Du, Z., Wilson, J.P., Yin, Z., Zhao, N., Wang, Y., Zhou, C., 2020. A new approach to modeling the fade-out threshold of coronavirus disease. Sci. Bull. 65, 1225–1227.

Yue T, Fan B, Zhao Y, Wilson, J.P., Du, Z., Wang, Q., Yin, X., Duan, X., Zhao, N., Fan, Z., Lin, H., Zhou, C. 2021. Dynamics of the COVID-19 basic reproduction numbers in different countries. Sci. Bull. 66, 229–232.

Zhang, X., Chen, X., Zhang, Z., Roy, A., She, Y., 2020. Strategies to trace back the origin of COVID-19. J. Infect. 80, e39–e40.